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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,532	12/11/2001	Alan Xi Huang	11134-005-999	4305

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,532	MEDINA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004 and 19 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-155 and 203-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136-139,142,143,145,147,149,153-155,205-208,211,212,214,215 and 217-226* is/are rejected.

7)☒ Claim(s) *140,141,144,146,148,150-152,203,204,209,210,213 and 216* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 2/19/04 and on remarks filed 1/8/04. Applicant has amended claims 136, 138, 139, and 154. Applicant has canceled claims 156-159, 162-170, 173-190, 193-197, and 202. Claims 205-226 are new. There are forty-four claims pending and forty-four under consideration. Claims 136-152, 205, and 206 are compound claims. Claims 153 and 207-216 are composition claims. Claims 154, 155, 203, 204, and 217-226 are use claims. This is the third action on the merits. The application concerns some pyrido[2,3-d]pyrimidine compounds, compositions, and uses thereof.

Response to Amendment

2. Applicants restriction of R^{14} in the formula of claim 136 to those recited in the priority document 60/296,499 means that claims 136-155, 203, 204, and 207-266 are afforded the priority date of 6/6/01, as discussed in point #3 of the previous office action. Applicants' cancellation of the affected claims renders moot the objection made in point #4. Applicants' cancellation of claims 187, 190, and 202 renders moot the indefiniteness rejection made in point #5.

Oath/Declaration

3. In view of the papers filed 1/8/04, the inventorship in this nonprovisional application has been changed by the deletion of Applicants Zhu and Marcus. The application will be forwarded to the Office of Initial Patent Examination (OIPE)

for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications upon which priority is claimed remains to lack adequate support under 35 U.S.C. 112 for claims 205 and 206 of this application. Provisional Application 60/296,499 differs because the R^{14} variable of each formula is restricted to five specific fused aromatic rings, not the present open-ended claim to aryl and heteroaryl.

Claim Rejections - 35 USC § 112

5. Claims 154 and 155 remain rejected and claims 217-226 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ

218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issue is the correlation between clinical efficacy for disease treatment and Applicants' single *in vitro* assay.

a) Determining if any particular claimed compound would treat any particular human disease would require synthesis of the compound, formulation into a suitable dosage form, and either subjecting it clinical trials with a number of fundamentally different diseases described below or subjecting it to testing in an art-recognized disease model, which is correlated to clinical efficacy. Considering the huge number of compounds embraced by claim 154 and the six distinct diseases to be tested, this would require a huge degree of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 30, page 24 to line 30, page 26, which merely states Applicants' intention to do so. Applicants describe formulations in line 29, page 21 to line 23, page 24. There are no working examples of any formulation required for the clinical practice of Applicants' invention. Possible routes of administration are taught in lines 31, page 26 to line 3, page 27. Possible doses and dosing schedules required to practice their invention are taught in lines 4 to 22, page 27. A 10,000-fold range of dosage is contemplated. Since no CXCR3 antagonist has ever been used to treat any human disease, how the skilled physician to know what dose to administer to

her patients? There is a single *in vitro* assay described in the passage spanning line 14, page 162 to line 14, page 163 with no data. Applicants have not asserted and it is not art-recognized that the results of this *in vitro* assay are correlated to clinical efficacy of any disease treatment. There is no art-recognized *in vivo* disease models used to test Applicants' compounds.

c) There is no working example of treatment of any disease in man or animals. There are no working examples of the formulations, doses, and dosing schedules required by the physician to practice Applicants' invention. d) The nature of the invention is clinical treatment of disease with antagonists of the CXCR3 receptor, which involves physiological activity. e) The state of the clinical arts with CXCR3 antagonists is provided by Carter (Curr. Opin. Chem. Biol.) who reports in Table 1, page 512, that mice lacking CXCR3 receptors are normal. In the paragraph spanning pages 513-514 elevated levels of this chemokine are reported in both psoriasis and MS patients, although no treatment of any such patients by antagonists of this chemokine were known in 2002. Table 3, page 516 makes clear that no CXCR3 antagonists were known in 2002. Thus, logically no diseases treatable by such antagonists could have been found by this date.

Onuffer (TRENDS in Pharm. Sci.) in Table page 460 reports MS, arthritis, sarcoidosis, allograph rejection, and cancer treatment as "possible therapeutic

indications". Thus, such treatments were speculative and not established in 2002. Table 2 and Table 3, pages 462 and 463 confirm that no CXCR3 antagonists were in clinical development in 2002. The only complete paragraph in column 2, page 462 reports that CXCR3 was the subject of drug development programs. Thus, in 2002 CXCR3 antagonists were still in the experimental stage and any claims of disease therapy are speculative in nature for which Applicants have provided no empirical support.

Proudfoot (Sem. Immun.) reports in the diagram on the top of page 59 that allograph rejection is the only "target" of CXCR3 ligand research. The first complete paragraph on page 61 states that inhibitors of only two the fifty chemokine receptors had progressed to clinical trials. Neither of these receptors was CXCR3. The last sentence in the paragraph states "[chemokines] have certainly been a difficult family to work with". Thus, in 2003, two years after Applicants filing date, only potential targets were art recognized and no therapeutic applications had been identified.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 136 as well as the hundred of diseases embraced by the term CXCR3 related disease. Thus, the scope of claims is very broad.

See *Ex parte Powers*, 220 USPQ 924 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP §2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. Thus, undue experimentation will be required to determine if any particular claimed compound is, in fact, a treatment of any disease.

Applicants argue that a utility rejection is improper, assert that "the selective expression of CXCR3 makes it an ideal target for intervention to interrupt inappropriate T-cell trafficking (page 3, lines 1-2), thus positive results of CXCR3 modulation in an assay such as described in the specification see pages 162-163 and Figure 19) are sufficiently convincing to those of skill in the art of the usefulness of a compound as claimed for the treatment of the recited diseases." and distinguish their application from the fact situation of *University of Rochester v. G.D. Searle & Co.,* 68 USPQ2d 1424 (DC WNY 2003). This is not convincing. To the first point, no utility rejection has been made and no enablement rejection concerning the making of the compounds has been made.

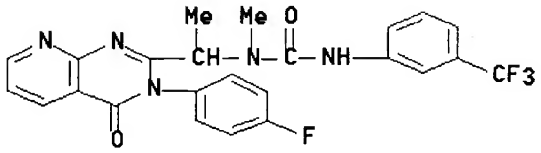
To the second point, assertion is not evidence and there is no evidence that the assay described on pages 162-163 has any correlation to clinical efficacy to treatment of any disease. To the third point, while Applicants have provided direction to the making of their compounds and have provided direction to the screening of these compounds in the assay discussed, there in no direction as to disease treatment. The case of University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003) at 1438 is cited to bolster point a) above concerning the amount of experimentation and the conclusion that the experimentation was undue. According to Judge Larimer, "[t]he fact that it took Searle about eight months to identify some PGHS-2 selective inhibitors, after screening over 600 compounds, however, does not show that the '780 application was enabling in the absence of undue experimentation." Applicants are urging the screening of millions of compounds in an assay not known to be correlated to disease treatment. *In vivo* and clinical evaluation of those millions of compounds makes the effort of Searle look like child's play.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 136-139, 142, 143, 145, 147, 149, 153, and 154 remain rejected and claims 205-208, 211, 212, 214, 215, 217, 218, 221, 222, 224, and 225 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Baxter ('005). The reference teaches the compound with registry number 330796-36-6 shown below. The Applicants claim the compounds with n = 0, X = C(O), R^{14} = 4-fluorophenyl, R^1 = methyl, R^2 = hydrogen, L-R^3 = CH_2-heteroaryl, L = the alkylene group CH_2, R^3 = heteroaryl, R^4 = 3-(trifluoromethyl)phenyl, and Q = C(O). The reference teaches such a compound with L-R^3 = CH_2-H, and R^4 = 3-(trifluoromethyl)phenyl-NH-. The compound is shown in the reference in lines 18-35, column 80. It is pictured in column 77 and is compound (20). The difference between the claimed and taught compounds is the urea rather than amide linkage to R^4 and the methyl group rather than alkylene-heteroaryl as L-R^3. These deficiencies are taught internally in the reference. Lines 30-31, column 32 teach that Applicants' claimed N-C(O)-linkage can replace urea linkage found in the working example (20). Alkylene-heteroaryl is taught as one of four possible substituents that would make up the R^8 radical in the reference in lines 50-56, column 30. This R^8 radical corresponds to Applicants L-R^3 radical.



Formulations are taught in lines 7-54, column 52. Thus, claims 153, 207, 208, 211, 212, 214, and 215 are made obvious. Treatment of psoriasis is taught in lines 1-15, column 51 of the reference. Thus, claims 154, 217, 218, 221, 222, 224, and 225 are made obvious.

Applicants argue that there is no suggestion to make the two changes discussed above and no motivation for doing so. This is not persuasive because the directions to make the changes are contained within the short Markush lists in the generic definitions taught in the reference. Firstly, the amide linkage was selected from a list of three possible linkages. The alkylene-heteroaryl is taught as one of four possible substituents. Even together this represents only twelve possible combinations. The medicinal chemist seeking to improve the potency and efficacy of his compounds can easily explore these twelve. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is found in the reference itself, in the short Markush lists described above.

7. Claims 136-139, 142, 143, 145, 147, 149, 153, and 154 remain rejected and claims 205-208, 211, 212, 214, 215, 217, 218, 221, 222, 224, and 225 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Baxter (WO 01/19800 A2, Ref AL). The compound taught by this reference was discussed above. It is found in lines 21-29, page 108. Claims 31-39 of the reference are drawn to the compound above and claim 37 provides the direction to replace the taught urea linkage with an amide linkage. Lines 5-8, page 123, claim 31 provide the teaching that alkylene-heteroaryl is one of four possible substituents that would make up the R^8 radical in the reference. Compositions are taught in claims 29 and 30 of the reference. Claims 1-28 of the reference are drawn to inhibiting altered growth states of cells and the meaning this teaching was discussed above, as was Applicants response.

Allowable Subject Matter

8. Claims 140, 141, 144, 146, 148, 150-152, 203, 204, 209, 210, 213, and 216 are objected to as being dependent upon a rejected base claim, but would be

allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please

direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact Mukund Shah SPE of 1624 at (571)-272-0674.

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TCMcK/me